

### DETAILED ACTION

1. **Claims 1-8 and 16-23 are pending.**
2. In response to the Notice of Panel Decision from Pre-Appeal Brief Review, the rejection of claims 1-8, 16 and 19-23 under 35 U.S.C. 103(a) as being unpatentable over Frankel ("Supplementation of Trace Elements in Parenteral Nutrition: Rationale and Recommendations") in view of Giordano et al (US 6,660,293) and claim 17 under 35 U.S.C. 103(a) as being unpatentable over Frankel in view of Giordano et al. and further in view of Ballevre et al. (US 2003/0161863) are withdrawn and a new grounds of rejection is set forth.

### *Claim Rejections - 35 USC § 103*

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.
4. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:
  1. Determining the scope and contents of the prior art.
  2. Ascertaining the differences between the prior art and the claims at issue.
  3. Resolving the level of ordinary skill in the pertinent art.
  4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

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claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. **Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frankel (“Supplementation of Trace Elements in Parenteral Nutrition: Rationale and Recommendations”).**

Regarding **claim 1**, Applicants claim a daily dose of 1-2 mg of selenium and 30-100 mg of zinc. The Examiner notes that Applicants do not require how much bulk material is provided as a carrier and in essence the composition on its most simple analysis is merely a ratio of the amount of selenium to that of zinc. Based on the claimed dose, the ratio of selenium to zinc claimed can be from 1:30 to 1:100.

Frankel discloses a total parenteral nutrition composition supplemented with trace elements including *a minimum provision* of 50 meg/day (i.e. 0.05 mg/day) and 10 mg/day of zinc (p. 587/ paragraph 4, p. 588/paragraph 6). Further, Frankel discloses that in cases of selenium depletion dose of 724 meg/day and 250 meg/day have been suggested (p. 587/paragraph 1 and 5). Frankel also discloses that while the AMA recommends 2.5-6 mg/day zinc, more can be used, for example as high as 1200 mg (p. 588/paragraphs 3 and 5).

Frankel clearly discloses the use of zinc in excess of selenium, the same way that Applicants have. While Frankel discloses the general relationship, the reference fails to disclose the exact ratios of Applicants components. However, it would have been obvious to one of

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ordinary skill in the art at the time of the invention to have produced a composition having zinc and selenium, in the claimed ratio in order to have the benefits of each of the trace elements while balancing the known risks.

Here, once a composition comprising the correct ratio is produced, one may administer any amount desired. The fact that Applicants claim a particular daily dose is intended use related to how a medical professional may administer the composition. The composition need only be required to meet that limitation, in this instance that would be solely based on the ratio of the components.

Regarding **claims 2-3 and 5**, modified Frankel discloses all of the claim limitations as set forth above. Given Frankel discloses a parenteral composition, it is clear that the composition is inherently an infusion solution that exists as an aqueous solution and is suitable for parenteral administration.

With respect to **claims 4, 7 and 8**, which relate to the concentration, amount or packaging of the composition, these limitations merely relate to how one can use the composition. The ratio of zinc and selenium is still the over riding issue related to administering the composition. With regards to dilution or concentration, it relates to how much of the composition one would have to administer to give the desired levels. The fact that Applicants may be giving more of the composition than suggested by Frankel has no bearing on the patentability of the composition claims. The compositions disclosed by Frankel could reasonably be made and packaged as claimed and still be used within the suggested guidelines in terms of RDA.

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Regarding **claim 6**, modified Frankel discloses all of the claim limitations as set forth above. Frankel also discloses total parenteral nutrition compositions comprising chromium and copper (p. 583/paragraphs 3-5, p. 584/paragraphs 1-9, p.585/paragraphs 1-4).

7. **Claims 16 and 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frankel (“Supplementation of Trace Elements in Parenteral Nutrition: Rationale and Recommendations” – Nutrition Research (1993) 13, p. 583-596) in view of Giordano et al. (US 6,660,293), Thomson et al. (“On supplementing the selenium intake of New Zealanders 1. Short experiments with large doses of selenite or selenomethionine” – Br. J. Nutr. (1978), 39, p. 579-587) and Sherratt et al. (US 6,523,349).**

Regarding **claims 16, 19, 21 and 22**, Frankel discloses administering a total parenteral nutrition composition supplemented with a *minimum provision* of 50 meg/day (i.e. 0.05 mg/day) of selenium and 10 mg/day of zinc to a human (p. 587/ paragraph 4, p. 588/paragraph 6). Further, Frankel discloses that in cases of selenium depletion doses of 724 meg/day and 250 meg/day have been suggested (p. 587/paragraph 1 and 5). Frankel discloses that the parental administration of iron is problematic and does not indicate supplementation of iron in total parenteral nutrition compositions (p.583/paragraph 3, p. 589/paragraphs 4-5).

While Frankel discloses a total parenteral nutrition composition supplemented with a recommended daily dose of 10 mg zinc and 250 meg of selenium, the reference does not explicitly disclose a zinc dosage of 30 mg/day to 100 mg/day or a selenium dosage of 1 mg-2 mg/day.

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Giordano et al. teach a nutrition supplementation composition comprising zinc in the range of about 20mg to about 30mg (Abstract, C3/L18-38). Giordano et al. disclose that the composition is used to treat nutritional deficiencies in patients suffering from a disease state that result in increased oxidative stress or elevated homocysteine levels (C3/L9-17).

Thomson et al. teach administering to a human 1 mg doses of selenium on each of five consecutive days (p. 580/Expt. 2A).

Given Giordano et al. teach zinc doses of about 20 mg to about 30 mg are known to be used in nutritional compositions and Thomson et al. teach selenium doses of 1 mg are known to be administered to humans for up to five days consecutively, it is clear that the prior art teaches that zinc doses ranging from 10 mg to about 30 mg and selenium doses of 1 mg can be administered to humans. Therefore, since the claimed daily dose of zinc ranging from 30mg to 100mg and selenium of 1 mg overlap that of the prior art, it would have been obvious to one of ordinary skill in the art at the time of the invention to have selected the overlapping portion of the ranges disclosed by the references because overlapping ranges have been held to be a *prima facie* case of obviousness. *In re Malagari*, 182 USPQ 549.

In the alternative, Sherratt et al. teach that the dosage of a therapeutic nutrient composition, comprising zinc and selenium, administered to a patient is guided by a physician skilled in the art on a case by case basis (C8/L47-67, C9/L42-43). Sherratt et al. teach that patients may receive multiple doses of a composition depending on the amount of the composition needed for the patients' particular condition, nutritional needs and body size (C9/L43-48).

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In this case, all of the factors taught by Sherratt et al. need to be taken into account when determining the dose of zinc and selenium required by a given individual.

There is a clear recognition that selenium is important in human nutrition primarily as a component for the enzyme glutathione peroxidase (GSH Px), an antioxidant which acts synergistically with vitamin E to protect cell membranes (Frankel p. 586/Selenium/paragraph 1). However, Frankel teaches that long term exposure can have severe negative side effects (p.587/pargraph 1). Frankel discloses the benefits of zinc as a component of zinc metalloenzymes (p. 587/Zinc/paragraph 1). Frankel et al. disclose that very high levels of zinc may be used with little negative effect (p.588/paragraph 5).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to have administered 1-2 mg of Se and 30-100 mg of zinc as a daily dose for a short period of time, i.e. 3-5 days as claimed, in order to have the beneficial effect of zinc and selenium. However, one would take extreme care and monitor the patient to make sure that the regime was discontinued before the negative side effects would out weight the positive ones.

Regarding **claim 20**, modified Frankel discloses all of the claim limitations as set forth above. Frankel also discloses administering a total parenteral nutrition composition further comprising chromium and/or copper (p. 583/paragraphs 3-5, p. 584/paragraphs 1-9, p.585/paragraphs 1-4).

Regarding **claim 23**, modified Frankel discloses all of the claim limitations as set forth above. Given Frankel disclose a nutritional composition used for the supplementation of trace elements which comprises chromium, copper, manganese, selenium and zinc (i.e. electrolytes), it necessarily follows that the electrolytes are in the form of electrolyte concentrates.

8. **Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Frankel (“Supplementation of Trace Elements in Parenteral Nutrition: Rationale and Recommendations” – Nutrition Research (1993) 13, p. 583-596) in view of Giordano et al. (US 6,660,293), Thomson et al. (“On supplementing the selenium intake of New Zealanders 1. Short experiments with large doses of selenite or selenomethionine” – Br. J. Nutr. (1978), 39, p. 579-587) and Sherratt et al. (US 6,523,349) as applied to claim 16, and further in view of Ballevre et al. (US 2003/0161863).**

Regarding **claim 17**, modified Frankel discloses all of the claim limitations as set forth above. While Frankel discloses administering a total parenteral nutrition composition comprising selenium and zinc to a human, the reference does not explicitly disclose that the human is an intensive care patient or a sepsis patient.

Ballevre et al. teach an enteral nutrition composition comprising about 40 to about 100 µg /dose of selenium and 5 to 10 mg/dose of zinc (Abstract, [0029]-[0030]) that is administered to critically ill patients including those with sepsis ([0005], [0011]). Further, Ballevre et al. discloses an enteral nutrition composition that does not comprise iron (*see* Example 1-[0048]-[0050]).

Given that Ballevre et al. teach that it was known to administer nutritional compositions comprising selenium and zinc to critically ill patients including those with sepsis, since Ballevre et al. teach a composition substantially similar to that of Frankel and that presently claimed, it would have been obvious to one of ordinary skill in the art to have administered the total parenteral nutrition composition of modified Frankel to critically ill patients including those with sepsis.

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***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELIZABETH GWARTNEY whose telephone number is (571)270-3874. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, D. Lawrence Tarazano can be reached on (571) 272-1515. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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